

OCTOBER 10, 2000

Study Reveals How Growth Factors Affect Human Stem Cells

Researchers have begun to probe the effects that growth factors have on the differentiation of human embryonic stem cells. According to the researchers, their efforts represent a step toward understanding how to direct human embryonic stem cells to become the more specialized cells that make up specific tissues such as brain and muscle.

In a research article published in the October 10, 2000, issue of *Proceedings of the National Academy of Sciences*, research teams led by Howard Hughes Medical Institute investigator Douglas A. Melton and Hebrew University geneticist Nissim Benvenisty report that they applied eight growth factors to cultured human embryonic stem cells to observe their effects on cell differentiation.

"While we have demonstrated the potential for directing the differentiation of these cells for use in cell replacement therapy, even in the best case, this represents only an initial step forward."

— Douglas A. Melton

Human embryonic stem cells are undifferentiated cells that can develop into any of the specialized cell types found in the human body. Their developmental fate is influenced by the activity of a number of cellular signals, including growth factors. "Until now, no one had reported extensive and systematic studies on human embryonic stem cells," said Melton, who is at Harvard University. Other research teams had performed similar studies on mouse embryonic stem cells, but Melton, Benvenisty and their colleagues saw the need to do a more comprehensive, systematic analysis of the effects of growth factors on the differentiation of human embryonic stem cells.

By applying each of the eight growth factors to the cultured stem cells, the researchers were able to follow the developmental path that the cells chose while under the influence of a specific growth factor. The studies showed that each of the growth factors elicited subtle differences in effect. While none of the growth factors unequivocally directed development of differentiation

toward a specific cell lineage, the studies hint that a combination and timing of growth factors might achieve such an end.

Melton emphasized that the choice of growth factors was a practical one and by no means represents the broad spectrum of growth factors that might govern stem cell differentiation. "While we have demonstrated the potential for directing the differentiation of these cells for use in cell replacement therapy, even in the best case, this represents only an initial step forward," he said. "Besides choosing those growth factors that were available, we chose those for which we could detect receptors on the surface of the cells. There was no sense in adding a growth factor if the cells didn't express a receptor for that growth factor."

The growth factors directed the stem cells to differentiate into three different categories: endodermal, ectodermal and mesodermal. Endodermal cells give rise to the liver and pancreas; ectodermal cells become brain, skin and adrenal tissues; and mesodermal cells become muscle. Furthermore, the researchers found that they could categorize the growth factors based on their effects on differentiation. One group of growth factors appeared to inhibit endodermal and ectodermal cells, but allowed differentiation into mesodermal cells. A second group induced differentiation into ectodermal and mesodermal cells, and a third group allowed differentiation into all three embryonic lineages.

"When an egg cell divides, it doesn't immediately tell its daughter cells to become nerve, brain or pancreatic cells," said Melton. "Rather, it first parses cells into the three general territories (germ layers) ectoderm, mesoderm and endoderm. And, our studies showed that the growth factors encourage cells to develop into more of one germ layer and less of the other two.

"In the best of all possible worlds, one would like to find growth factors could be added to a human embryonic stem cell to make it become a cardiomyocyte to replace defective heart muscle or a pancreatic beta cell for transplantation into diabetics," said Melton. "But these studies strongly suggest that finding such a factor will be exceedingly unlikely."

Also, said Melton, the finding that most of the growth factors inhibit differentiation of specific cell types suggests that use of growth factor inhibitors might prove as important as inducers in directing stem cell differentiation. Ultimately, he said, controlling stem cell differentiation will likely involve a strategy that employs multiple growth factors in a certain order and at certain times.

"It may be a bit like educating a child, in which you don't designate children in kindergarten as doctors, lawyers or surgeons, but you give them some kind of general education. And, as they progress and show an interest in a specific field, you give them a more specialized education."